REMARKS

The Applicants thank Examiner Dana Shin for her time and useful suggestions during her interview with Applicants' representative, Cheryl H. Agris and one of the inventors, Dr. James Donegan on March 25, 2010. The substance of the interview is set forth below.

Claim 275 has been amended to more distinctly claim that which Applicants regard as the invention. Amended claim 275 is supported by the specification (for example, see the paragraph bridging pages 70-71, the paragraph bridging pages 73-74 and examples 16-18, pages 141-145). No new matter has been added.

I. SUBSTANCE OF INTERVIEW

A. Brief Description of any Exhibit Shown or any Demonstration Conducted

Applicants submitted Figures 21-23 of the specification since these figures were used in distinguishing the claimed invention from the prior art.

B. Identification of Claims Discussed

Claims 275, 296 and 297 were discussed.

C. Identification of Specific Prior Art Discussed

As will be set forth in further detail below, Engelhardt et al. (US 5,260,433) (hereinafter "Engelhardt") and Myers, EP0273085 (hereinafter "Myers") were discussed with respect to the rejection under 35 USC §102(b); Osborne et al. *(PNAS, 1976,* 73 :4536-4540) (hereinafter "Osborne") and Engelhardt were discussed with respect to the rejection under 35 USC §103 and Alul, US Patent No. 5,532,130 (hereinafter "Alul") was discussed with respect to the rejection under 35 USC §102(e).

D. Identification of Principal Proposed Amendments of a Substantive Nature Discussed

Amendments to claim 275 were discussed.

E. Identification of General Thrust of Principal Arguments presented to the examiner

The claimed compositions are not anticipated are or obvious over the cited prior art.

F. A General Indication of Any other Pertinent Matters Discussed

No other pertinent matters were discussed.

G. General Results or Outcome of the Interview

Applicants will in the written response present the amendments and arguments made during the interview.

II. The Rejections Under 35 USC §102(b)

Claims 275 and 296 have been rejected over Engelhardt and claim 275 has been rejected over Myers. The rejections and responses are set forth in detail below.

A. Engelhardt

Claims 275 and 296 have been rejected under 35 USC §102(b) over Engelhardt. Applicants respectfully traverse the rejection since Engelhardt does not disclose each and every element of the amended claim 275. Claim 275, as amended, recites that the monomeric unit comprises two elements covalently attached to one another: (1) **a protein that is a ligand to a cell surface receptor** and (2) a single-stranded polynucleotide. As will be discussed in further detail below, there is no disclosure in Englehardt of a **protein ligand** to a cell surface receptor. Hormones disclosed in Engelhardt are small molecules not proteins. Applicants further note that amended claim 275 is directed to an isolated composition that comprises nucleic acids hybridized to each other. In contrast, the Engelhardt compositions are completely single-stranded. These become double-stranded after hybridization to complementary sequences in a specimen. However, in this form they can no longer be considered to be

"isolated" as they are now part of a mixture of hybridized and unhybridized nucleic acids from the specimen.

Applicants further wish to respond to specific assertions made in the Office Action. The Office Action specifically states on page 3:

> Applicant argues that the claims are not anticipated because Engelhardt et al. do not teach an essential element: the presence of proteins that are covalently bound to a nucleic acid.

In response, Applicants wish to clarify that Engelhardt et al. do not teach an essential element: the presence of protein ligands to a cell surface receptor that are covalently bound to a nucleic acid. In Example V of Engelhardt, poly-L-lysine was added to DNA and in Example VII of Engelhardt, cytochrome C was added to DNA. A protein ligand to a cell surface receptor is not used in either of these cases. As such, Applicants still maintain that Engelhardt neither uses nor advocates the use of protein ligands to a cellular receptor.

The Office Action further states on page 3:

> ……. it is found that the meaning of "covalent bonding" or "covalent attachment" is described in the instant specification such that the covalent bonding or attachment between a protein and a nucleic acid can be made by chemical methods described in Engelhardt et ai. (US 5,260,433), which is fully incorporated in the instant specification by reference. Further, the specification also states that ligands (proteins) can be attached to the nucleic acid as described in Engelhardt et al. (US 5,260,433). See pages 39-40 and 59. Note that the Engelhardt et al. (US 5,260,433) is the very prior art reference applied in the instant rejection. Hence, applicant explicitly acknowledges through the explicit disclosure in the specification that covalent attachment between protein and a polynucleotide can be made as taught and described by Engelhardt et ai. (US 5,260,433), which therefore suggests that the allegedly missing essential element "the presence of proteins that are covalently bound to a nucleic acid" is logically and necessarily disclosed in the prior art of Engelhardt et ai. (US 5,260,433)……

Applicants disagree. Although the methods of Engelhardt have been cited in the disclosure as being adapted to provide teachings on how to create a construct of the present invention, Engelhardt itself does not describe such a construct.

The Office Action on page 4 states:

> ....Applicant argues that the proteins disclosed in Engelhardt et al. are not ligands that bind to cell surface receptors by pointing out column 24 that the only proteins disclosed are enzymes as possible Sig moieties. Contrary to applicant's argument, the disclosure of Engelhardt et al. is not limited to Sig moieties or enzymes. As stated above, the Engelhardt et al. patent discloses that as a general principle one can make a hybrid construct comprising a protein ligand and a polynucleotide by covalently attaching the ligand and the polynucleotide. Engelhardt et al. also teach that hormone (protein) ligand binds its cognate receptor. See column 26, lines 44-49. Applicant argues that the content of column 26 shows that the ligands are referred to as small organic molecules and not proteins. It is found that the term "protein" claimed and used in the instant application embraces "an antibody, a hormone, a growth factor, a lymphokine or cytokine and a cellular matrix protein" as defined by applicant. See for example original claim 91 and pages 42 and 53 of the specification. Hence, given the broadest, reasonable interpretation in light of the applicant-defined definitions and teachings of the instant specification, the "hormone" in Engelhardt et al. is within the meaning of the "protein" as defined by applicant and as intended and claimed by applicant and thus read on the claimed "protein" (see claim 275), which is claimed to be a hormone (see claim 296). Further, Engelhardt et al. teach that example 3 pertaining to hormone receptors shows "the ligand bound to the nucleic acid reacts with a naturally occurring protein." See column 26, lines 61-64.

Applicants respectfully disagree. First, Applicants further take issue with the assertion that Engelhardt et al., teach this as “a general principle” since there is no specific teaching of covalent attachment to a nucleic acid with a protein ligand to a cell surface receptor. Further as noted above, on page 4, the Office

Action also makes reference to "Engelhardt et al. also teach that hormone (protein) ligand binds to its cognate receptor." Applicants, in response, respectfully point out that hormones as a class encompasses a wide variety of different molecules. Engelhardt et al. has voluntarily restricted themselves to hormones that are small organic molecules. Specifically, Engelhardt states in column 26, lines 44-46 "Hormone receptors and other receptors on the surface of the cell to which organic molecules will specifically bind". It should be noted that the exemplifications of column 26 are introduced in a passage above as "The detection of nucleic acids to which specific molecules have been covalently attached can be effected through the use of many naturally occurring proteins to which small molecules are know to bind." (Column 26 lines 13-16 and emphasis added). The hormone/hormone example is then used as an illustration of this concept. On the other hand, even though the protein ligand recited in claim 275 can be a hormone (claim 296), it must be a protein and the claim (even broadly interpreted) does not encompass ligands that are not proteins (such as small organic molecules). For instance, the epinephrine ligand example used for a hormone in column 26 of Engelhardt et al., would not be within the scope of pending claims 275 and 296. As such, Applicants do not believe that there is overlap between the hormones used in Engelhardt et al. and in the subject matter claimed where it is improper to expand the protein ligand of the present claims to somehow include molecules that are not proteins (i.e small organic molecules) and it is improper to expand the small organic molecule hormones of Engelhardt to include proteins.

The Office Action on page 5 further states:

> Applicant argues that there is no disclosure of attaching a protein ligand to an A:U double-stranded polynucleotide and that Engelhardt et al. only disclosed modified nucleotides containing the Sig moiety. First, as stated above, Engelhardt et al. disclosed the concept of "the ligand bound to the nucleic acid reacts with a naturally occurring protein." See column 26, lines 61-64. Second, with regard to the nucleic acid, Engelhardt et al. teach that it can be a double-stranded polynucleotide of DNA or RNA

> such as A:U polynucleotide, which can function as an interferon stimulator. In fact, Engelhardt et al. teach the advantage of using the A:U double-stranded polynucleotide because it "would be more effective and more powerful in inducing or stimulating agents for the production on interferon and related materials from cells." See column 27, lines 16-43. Third, even if the Sig moiety is included in the ligand bound to double-stranded A:U polynucleotide, there is no language in the claims that excludes the Sig moiety.

Applicants, in response, note that Examples VIII and IX in columns 5 and 6 strictly use biotin as the ligand in the polyA/U double-stranded DNA molecules. Even assuming *arguendo* that from these examples other modifications described in Engelhardt et al. could have been made with respect to poly A/U, this concept is still restricted to the use of small organic molecules as the ligands and does not describe the use of protein ligands to a cellular receptor.

In view of the above arguments, Applicants assert that the rejection over Engelhardt under 35 USC 102 has been overcome. Therefore, Applicants respectfully request that the rejections be withdrawn.

B. Myers

Claim 275 remains rejected under 35 U.S.C. 102(b) as being anticipated by Myers. The Office Action states:

> Applicant argues that the structure taught in Myers is different from that of instantly claimed invention such that the Myers monomeric units are hybridized to each other rather than to a common matrix polynucleotide. It is noted that the binding matrix claimed in the instant case does not exclude the presence of a protein as the claim recites "said binding matrix is a polynucleotide comprising sequences", wherein the "comprising" is an open-end transitional phrase and thus can include a protein. Further, Myers taught *"one or more* selected foreign polynucleotides (nucleic acids such as DNA or RNA)" or "pieces of nucleic acid" to which a ligand is chemically coupled, wherein the polynucleotides are duplex DNA. See claims 1-2 for example. Hence,

> Myers taught "more than one monomeric unit" comprising a protein covalently attached to a single-stranded polynucleotide, wherein more than one monomeric unit is bound to a complementary polynucleotide.

Applicants respectfully traverse the rejection. The language of pending claim 275 requires that more than one monomeric unit be hybridized to **a** matrix, i.e. a single matrix forms the scaffold for binding of multiple monomeric units. ("each monomeric unit is attached to a binding matrix"). As such, Applicants assert that the illustration of Figure 2 in Myers does not provide an example of the present invention, where there are supposed to be multiple monomeric units hybridized to a matrix. However, in order to more distinctly recited the subject matter of the invention and to advance prosecution, claim 275 has been amended to read:

> "….. multimeric composition comprising **a binding matrix and** more than one monomeric unit……and wherein each monomeric unit is **separately** attached to **said** binding matrix….."

As noted above, this language is clearly supported by Figures 22 and 23 of the specification and it clarifies the relationships between the monomeric units and the matrix that binds them together.

Applicants would also like to point out that comments on page 6 concerning "one or more selected polynucleotides" in Myers does not give any indication that they are part of a construct as recited in amended claim 275. The referenced Claims 1 and 2 of Myers do not give any particular indication that they describe multiple monomeric units (containing ligands) hybridized to a single nucleic acid strand. The broadest reasonable reading of the claim is that there are individual complexes made for various nucleic acids of interest. The claims should also be read in light of the specification. In column 2, the use of more than one nucleic acid is described in the context of "co-transfection". Two methods are given for this process. In column 2 lines 21-25, it is stated that "when effecting a co-transfection with two or more different polynucleotides, for instance, fragments a and b, these fragments can be introduced by linking them **separately** to the target vectors." (emphasis added and target vectors refer to a

ligand to a receptor.) Clearly it can be seen that in Myers, two separate and independent conjugates are formed (Seq a-ligand and Seq b-ligand). According to the methods described in Myers, double-stranded versions of such molecules would only be two separate sequences with a ligand at each end. Thus, no description is provided for joining them together into a multimeric complex and this is not a description of a construct that would be represented by the language of claim 275. In a second method in column 2, lines 25-26, "Alternatively a and b can be linked together on a same vector unit." Pictorially, this can be represented as (Seq a-ligand-Seq b). A single ligand is used to join two separate nucleic acid sequences. This again does not represent the multimeric construct of claim 275. In conclusion, even when more than one nucleic acid fragment or piece is used by Myers, there is no description of a relationship between these fragments that would allow one to envision the complex described in pending claim 275.

In view of the amendment of claim 275 and the above arguments, Applicants assert that the rejection of claim 275 under 35 USC 102(b) over Myers has been overcome. Therefore, Applicants respectfully request that the rejection be withdrawn.

III. The Rejection Under 35 USC §103

Claims 275 and 296-297 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Engelhardt and Osborne.

> Applicant argues that there is no motivation to apply the teachings of Engelhardt et al. to the method of Osborne et al. Contrary to applicant's argument, this rejection is not based on applying Engelhardt et al. to Osborne et al. Rather, the instant rejection is based on incorporating the teachings of Osborne et al. into the teachings of Engelhardt et al. such that the insulin that specifically interacts with insulin receptor is incorporated as the protein ligand that is present in the composition of Engelhardt et al. Applicant further argues that no protein hormones are described in Engelhardt et al. and the Engelhardt et al. reference relates to SIG moieties for signal detection. Contrary

> to applicant's argument, as detailed above, the ligand or hormone disclosed in Engelhardt et al. is within the applicant-defined meaning of ligand or hormone. ….. Further, as stated above, the SIG moieties exemplified in Engelhardt et al. are not the only disclosure described in Engelhardt et al. as the Engelhardt et al. is a patent literature describing wide range of biological principles.

Applicants respectfully traverse the rejection. Given that the Osborne reference was published many years before the Engelhardt et al., and well known in the art prior to the submission it is hard to understand why it would be obvious to combine the Osborne reference with the teachings with Engelhardt et al. even in view of the KSR Decision. Even under the totality of the circumstances test, it would not have occurred to one of ordinary skill in the art to combine these two references. As noted above, Osborne was published several years prior to Engelhardt and was readily available to Engelhardt et al. but was not used.

Furthermore, Englehardt taught away from using large macromolecules such as insulin as a choice for a hormone ligand in their system. As discussed above, Applicants take issue with the opinion of the Office Action that in general, Engelhardt et al. embraces the use of proteins hormones as ligands. Part of the rationale for the emphasis on "small" by Engelhardt is revealed in a discussion of a ligand (such as a hormone) in column 26, lines 18-21. "These nucleotides are then incorporated into specific nucleic acids using a DNA or RNA polymerase or ligase reaction or a chemical linkage." Thus although chemical linkages may not be affected by size, the use of enzymatic processes (such as with a polymerase or ligase) could be affected by nucleotides that have large groups attached. Given the complex of Engelhardt's purpose, one of ordinary skill in the art would not have been disposed to attach insulin. Consequently, there is a deliberate teaching away of the use of proteins (such as insulin) that would not render obvious the application of macromolecules such as insulin or any other protein hormone as a ligand to be applied to the method of Engelhardt et al.

The Office Action further states:

> Applicant further argues that the A:U polynucleotide of Engelhardt et al. is used to stimulate immune responses, which is not suitable for using insulin. However, applicant has failed to provide reasons why combining immune stimulatory A:U polypeptide with insulin is unsuitable for using insulin. Contrary to applicant's argument, one of ordinary skill in the art wanting to provide insulin, for example to treat diabetic patients, may want to also stimulate immune responses in the diabetic patients for various reasons such as in the case when the patients need to have stimulated immune system for their specific physiological conditions. Applicant argues that Osborn does not provide motivation to obtain multimerized insulin. In response, it is noted that the *KSR* decision forecloses the argument that a specific teaching, suggestion or motivation is required to support a finding of obviousness…. Further, although Osborne does not teach multimerized insulin, it would have been apparent to one of ordinary skill in the art wanting to deliver more than one insulin unit to recognize making a composition with multiple insulin units would provide convenience as such composition would not necessitate making multiple compositions comprising a single insulin unit. Applicant argues that even if there were motivation, one cannot arrive at the claimed composition because Engelhardt fails to teach the structure of the claimed composition. Contrary to applicant's argument, the teachings of Engelhardt et al. provide the claimed structure ….and sufficient information and knowledge to make the claimed structure.

Applicants, in response, wish to make two points. In the first place, diabetes is often considered to be an autoimmune disease. As such, the concept that heightened immune stimulation should be induced in a subject that has a pre-existing overstimulation seems rather contra-indicative. Secondly, if there had been evidence in the literature at the time of the filing that such a seemingly self-defeating therapy was actually beneficial, this would only render obvious co-administration of A:U and insulin together, without providing any particular motivation to have the insulin covalently linked to at least one of the strands..

No particular clue is given in Engelhardt that the effectiveness of insulin itself would be increased if A:U and insulin were covalently linked together.

Applicants further take issue with the statement "making a composition with multiple insulin units would provide **convenience** as such composition would not necessitate making multiple compositions comprising a single insulin unit." (Emphasis added) This is somewhat circular logic in that making the multimeric complex in itself requires providing and using single insulin units to make the multimerized form. In addition other steps such as adding a nucleic acid to the insulin and carrying out hybridization is required, consequently to a manufacturer preparing multimerized insulin. These extra steps would be considered to be an inconvenience rather than a convenience, but this inconvenience would be outweighed by generating a product that ultimately had superior properties compared to the monomeric form of insulin. To a user, no particular convenience is achieved in delivering multimerized insulin compared to the singular form of insulin, since both represent pre-formed reagents.

In view of the above arguments, Applicants assert that the rejections under 35 USC §103 have been overcome. Therefore, Applicants respectfully request that the rejections be withdrawn.

IV. The Rejections Under 35 USC §102(e)

Claim 275 has been rejected under 35 U.S.C. §102(e) as being anticipated by Alul. The Office Action specifically states:

> Alul discloses an oligonucleotide of 25 nucleotides in length covalently bonded to one or more ligand molecules specific to a cell surface receptor, wherein the oligonucleotide is hybridized to its complementary oligonucleotide sequence. …..Note that the term polynucleotide recited in the instant claims means two or more chains of DNA or RNA. Hence, the oligonucleotide of 25 nucleotides in length of Alul necessarily comprises more than one units of polynucleotides attached to a ligand, thereby forming a multiple units of polynucleotides covalently attached to ligands, wherein the multiple units are hybridized to

a complementary polynucleotide. Accordingly, Alul discloses the structure of the claimed invention.

Applicants respectfully traverse the rejection. First, Applicants respectfully point out that in a cell it is understood that the anti-sense of Alul is intended to hybridize to a target mRNA, and thereby generate a composition that is double-stranded, i.e comprising two strands of nucleic acids. However, the complex of Alul is certainly not an isolated complex, the complex recited in claim 275.

Secondly, Applicants are uncertain as how the term "polynucleotide" (used in the singular) "means two or more chains" and "necessarily" provides a description of "multiple units of polynucleotides covalently attached to ligands". the term "polynucleotide" is never used in the Alul claims and only the term "oligonucleotide" is used. For the purposes of argument, Applicants will assume that these terms are intended to be used interchangeably in the Office Action. In contrast to the viewpoint in the Office Action, Applicants would assert that the claims in Alul continuously recite "said oligonucleotide chemically modified at least one site" and does not contain the language at "one or more sites". As is, there is only a description of a single modification per oligonucleotide. Since the particular motivation for the presence of the ligand in Alul is to enhance the introduction of the modified oligonucleotide into a cell, it may be that a single modification was deemed to be necessary and sufficient to fulfill this function. Similar language is seen in the beginning of the Summary of the invention "……hybridizing at least one 2'-5' oligonucleotide in a sequence specific manner to complementary mRNA or complementary duplex DNA."

In view of the above arguments and the amendment of claim 275, Applicants assert that the rejection over Alul under 35 USC §102(e) has been overcome. Therefore, Applicants respectfully request that the rejection be withdrawn.

SUMMARY AND CONCLUSIONS

It is Applicants belief that the pending claims are in condition for allowance. However, if a telephone conversation would further the prosecution

of the present application, Applicants' undersigned attorney request that he be contacted at the number provided below.

Respectfully submitted,

/Cheryl H Agris/

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